IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CAREDX, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,	)	
Plaintiffs,	)	
v.	)	C.A. No. 19-567 (CFC)
NATERA, INC.,	)	
Defendant.	)	

DEFENDANT NATERA INC.'S OPENING BRIEF IN SUPPORT OF ITS MOTION TO DISMISS PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 12(b)(6)

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I. NATURE AND STAGE OF THE PROCEEDINGS

Plaintiffs CareDx, Inc. ("CareDx") and The Board Of Trustees Of The Leland Stanford Junior University ("Stanford," and collectively with CareDx "Plaintiffs") filed their complaint on March 26, 2019 (the "Complaint"). D.I. 1. Pursuant to Fed. R. Civ. P. 12(b)(6), Natera files this motion to dismiss the Complaint for failure to state a claim upon which relief can be granted.

II. SUMMARY OF THE ARGUMENT

Plaintiffs allege that Natera's Kidney Transplant Rejection Test ("Kidney Test") infringes U.S. Patent Nos. 9,845,497 ("'497 patent"), Ex. A,[1] and 8,703,652 ("'652 patent"), Ex. B (the "Patents").[2] But Plaintiffs cannot show they are entitled to relief for at least two reasons.

First, the claims of the Patents are invalid because they claim unpatentable subject matter under 35 U.S.C. § 101. It is well-settled that "laws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 70 (2012) (internal quotation marks and citations omitted). Yet the Patents rest entirely on observing natural phenomena inherent to organ transplants: the presence of an organ donor's nucleic acids (such as DNA) in the transplant recipient's circulation (such as blood), and a correlation of that presence to rejection of the transplanted organ by the recipient's body. They claim nothing more than the detection and use of these phenomena by conventional methods well known in the art, which is not patentable. The claims begin and end with nucleic acids and their correlation to disease, both of which are natural phenomena, and they therefore claim ineligible subject matter. *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015) ("The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring.").

[1] Citations to "Ex." refer to exhibits to the Declaration of Sandra L. Haberny, filed herewith.
[2] The Patents have a common written description, and one independent claim each.

Second, Plaintiffs' contention that Natera's Kidney Test infringes the '652 patent should be dismissed under *Ashcroft v. Iqbal*, 556 U.S. 662 (2009), and *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544 (2007), for failure to state facts plausibly entitling them to relief. Specifically, Plaintiffs fail to allege facts plausibly showing that Natera's Kidney Test practices a critical element of the sole independent claim (claim 1) of the '652 patent. Claim 1 element (d) requires that "sensitivity of the method is greater than 56% ***compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)***." *See* Ex. B, at 27:67-28:40.[3] This requirement was added during prosecution to overcome prior art, and therefore limited the scope of the claims. Yet, Plaintiffs now accuse Natera of using technologies within the scope of that prior art to support their infringement claims. The complaint recites no facts showing any ***comparison*** of the sensitivity of Natera's ***Kidney*** Test to anything at all—much less a literal comparison to the claimed method for surveillance of a ***cardiac*** disorder. Nor can Plaintiffs ever show this because Natera's Kidney Test does not involve any such comparison. Plaintiffs thus have not made a plausible showing of literal infringement, and prosecution history estoppel bars them from arguing Natera infringes under a doctrine of equivalents theory. The infringement claim likewise fails.

These deficiencies cannot be cured through amendment. Plaintiffs cannot show entitlement to relief, and the complaint should be dismissed with prejudice in its entirety.

III. STATEMENT OF FACTS

A. The Claims Of The Patents

Independent claim 1 of the '652 patent, Ex. B, at 27:38-29:20, recites the following steps:

> 1. A method for detecting transplant rejection, graft dysfunction, or organ failure, the method comprising:
>
> > (a) ***providing a sample comprising cell-free nucleic acids*** from a subject who has received a transplant from a donor;

[3] All emphases are added unless otherwise noted.

(b) ***obtaining a genotype*** of donor-specific polymorphisms or a genotype of subject-specific polymorphisms, or obtaining both a genotype of donor-specific polymorphisms and subject-specific polymorphisms, ***to establish a polymorphism profile for detecting donor cell-free nucleic acids***, wherein at least one single nucleotide polymorphism (SNP) is homozygous for the subject if the genotype comprises subject-specific polymorphisms comprising SNPs;

(c) ***multiplex sequencing*** of the cell-free nucleic acids in the sample ***followed by analysis of the sequencing results using the polymorphism profile*** to detect donor cell-free nucleic acids and subject cell-free nucleic acids; and

(d) ***diagnosing, predicting, or monitoring a transplant status or outcome*** of the subject who has received the transplant ***by determining a quantity of the donor cell-free nucleic acids*** based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids by the multiplexed sequencing, wherein an ***increase in the quantity of the donor cell-free nucleic acids over time is indicative of transplant rejection, graft dysfunction or organ failure***, and wherein ***sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)***.

Independent claim 1 of the '497 patent, Ex. A, at 28:1-30:61, recites the following steps:

1. A method of detecting donor-specific circulating cell-free nucleic acids in a solid organ transplant recipient, the method comprising:

(a) ***genotyping a solid organ transplant donor*** to obtain a single nucleotide polymorphism (SNP) profile of the solid organ transplant donor;

(b) ***genotyping a solid organ transplant recipient*** to obtain a SNP profile of the solid organ transplant recipient, wherein the solid organ transplant recipient is selected from the group consisting of: a kidney transplant, a heart transplant, a liver transplant, a pancreas transplant, a lung transplant, a skin transplant, and any combination thereof;

(c) ***obtaining a biological sample from the solid organ transplant recipient*** after the solid organ transplant recipient has received the solid organ transplant from the solid organ transplant donor, wherein the biological sample is selected from the group consisting of blood, serum and plasma, and wherein the biological sample comprises circulating cell-free nucleic acids from the solid organ transplant; and

(d) ***determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample*** by detecting a homozygous or a heterozygous SNP within the donor-specific circulating cell-free nucleic acids from the solid organ transplant in at least one assay, ***wherein the at least one assay comprises high-throughput sequencing or digital polymerase chain reaction (dPCR),*** and wherein the at least one assay detects the donor-specific circulating cell-

> free nucleic acids from the solid organ transplant ***when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids*** in the biological sample.

B. The Claims Of The Patents Are Directed To Natural Phenomena

The Patents are directed to analyzing naturally occurring biological molecules (here, nucleic acids) in organ transplant recipients. The pertinent properties of nucleic acids are well-accepted scientific principles. *See, e.g.*, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580-82 (2013). Nucleic acids, such as deoxyribonucleic acid ("DNA"), typically exist inside of cells. *Id.* at 582. They encode genetic information necessary for building and maintaining cells and making them function. The building blocks of nucleic acids, called "nucleotides," store genetic information in the form of ordered "sequences," which describe unique series of nucleotide bases that make up an individual's genes. *Id.* at 580-81. The genes in aggregate comprise the individual's "genome," and naturally occurring variations in the sequences differentiate individuals. *Id.* The Patents do not alter these inherent principles in any way.

The common disclosure of the Patents acknowledges that nucleic acids can be found outside cells, and that such "cell-free" nucleic acids (e.g., in circulating blood) are a well-known natural phenomenon. The Patents also acknowledge that it is well-known that cell-free nucleic acids are the product of diseases involving death, or "apoptosis," of cells containing the nucleic acids, and that this occurs in cancer and in transplant rejection. Ex. B, at 6:57-67 ("Circulating, or cell-free, DNA was first detected in human blood plasma in 1948. … Since then, its connection to disease has been established in several areas. … Studies reveal that much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells … and greatly elevated levels of nucleic acids from apoptosis is observed in diseases such as cancer. …"); 7:40-46 ("[A]s cell-free DNA or RNA often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients…"). As the common

disclosure makes clear, "[i]n all these applications of circulating nucleic acids, the presence of sequences differing from a patient's normal genotype has been used to detect disease." *Id.* at 7:30-32. Thus, detecting nucleic acids that originated from the donor organ in a transplant recipient's circulation is simply a matter of observing a natural phenomenon: the presence of nucleic acids different from those normally present in the recipient's circulation. *See also id*. at 6:67-7:16; 7:19-29; 7:40-46; 8:18-21.

The Patents recount various ways that nucleic acid sequences of a transplant donor and recipient may differ, including by what are called "polymorphisms." According to the Patents, "[a] polymorphism refers to the occurrence of two or more genetically determined alternative sequences or alleles in a population." *Id.* at 11:24-26. The Patents disclose that "[a] polymorphism between two nucleic acids can occur ***naturally***…." *Id.* at 11:39-44. The Patents also disclose various types of polymorphisms, including "single nucleotide polymorphisms (SNP's)," which are DNA sequences that differ between individuals at a single nucleotide position.

The Patents cite numerous references from to the 1990's disclosing that "as cell-free DNA or RNA often arises from apoptotic (*i.e.,* dying) cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming [sic] organ failure in transplant patients…." *Id.* at 7:41-46. The Patents also provide examples of how such techniques could be used to make diagnoses based upon donor-derived cell-free nucleic acids in a transplant recipient's circulation. *Id.* at 7:47-8:21. The Patents explain that "for heart transplant patients, donor-derived DNA present in [blood] plasma can serve as a potential marker for the onset of organ failure." *Id.* at 8:18-21.

The Patents acknowledge that donor-specific cell-free nucleic acids in a transplant recipient's circulation and their correlation to transplant rejection are Nature's handiwork.

C. Amendment To Add Sensitivity Limitation

The '652 patent describes monitoring transplant rejection, and discloses only one application of this – monitoring a heart condition called cardiac allograft vasculopathy ("CAV"). Ex. B, at 5:54-6:55; *see also id.* at 6:1-3. The '652 patent discloses that "[c]urrent surveillance methods for CAV lack adequate sensitivity or require invasive procedures and the most commonly applied method, coronary angiography, lacks sensitivity." *Id.* at 6:8-12. The '652 patent incorporates by reference, *id.* at 3:3-7, a publication by Kobashigawa, J.A., *et al*. ("Kobashigawa"), which describes these "current surveillance methods," particularly the "most commonly applied method, coronary angiography," *id.* at 6:8-12. Kobashigawa explains that this technique is an "intravascular ultrasound" that "is an invasive procedure that detects thickening in the walls of the coronary arteries," and "provides a sonar image of intimal and media thickness." Ex. E, at 1532.

As issued, claim 1(d) of the '652 patent recites, in pertinent part, "wherein sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)." Ex. B, at 27:67-28:40. The patent Examiner added the clause "***compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)***" to then-claim 36 (which became claim 1), following an interview with the applicant, in order to overcome prior art and secure allowance. Ex. F, at 4-5; Ex. G, at 2 (showing prior claim language lacking amendment). The Examiner's "Reasons for Allowance," Ex. F, at 3, state:

> By amendment to the claims, Applicant has persuaded the Examiner that the prior art … alone or in combination, do not teach or disclose a method for detecting transplant rejection, graft dysfunction, or organ failure . . . wherein the sensitivity of the method ***is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)***.

D. Natera's Accused Kidney Test

Plaintiffs allege that Natera is infringing their Patents by "market[ing] and sell[ing] a Kidney Transplant Rejection Test." D.I. 1, at ¶ 10. Pertinent here, Plaintiffs allege that Natera's Kidney Test

infringes '652 patent claim element 1(d), which requires that "sensitivity of the method is greater than 56% ***compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)***." Ex. B, at 27:67-28:40. But the Complaint makes no allegation of any comparison to the sensitivity anything, much less that of a surveillance method for a heart condition, such as CAV. At most, the complaint alleges stand-alone measures of Natera's Kidney Test's sensitivity for detecting kidney transplant rejection. D.I. 1, at ¶ 24; *id.*, Ex. 8, at 7-8.

IV. LEGAL STANDARD

A. Natural Phenomena Are Not Patentable

"[L]aws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo,* 566 U.S. at 70. "The inventive concept [of a claim] cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself." *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016). "[S]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Mayo*, 566 U.S. at 82. And "[t]he prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the [abstract idea] to a particular technological environment or adding insignificant post solution activity." *Id.* at 73. Only "innovative" or "inventive" uses of natural phenomena are afforded patent protection. *Myriad*, 569 U.S. at 595 ("Had Myriad created an innovative method of manipulating genes while searching for the [natural] genes, it could possibly have sought a method patent."); *Parker v. Flook*, 437 U.S. 584, 594 (1978) ("[A]n inventive application of the principle may be patented.").

According to the *Mayo* framework, patent claims are ineligible for protection if they: (1) are directed to a patent-ineligible concept and (2) fail to recite additional elements constituting an inventive concept "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Mayo*, 566 U.S. at 72-73, 77-80; *Ariosa*, 788 F.3d at 1375.

Importantly, "[t]he inventive concept necessary at step two of the *Mayo*/*Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself. That is, under the *Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility." *Genetic Techs.*, 818 F.3d at 1376.

Patentability under 35 U.S.C. § 101 is a threshold legal issue that must be answered early in a case. *Bilski v. Kappos*, 561 U.S. 593, 602 (2010)); *see also Ultramercial, Inc. v. Hulu, LLC*, 772 F.3d 709, 717, 718 (Fed. Cir. 2014) (Mayer, J., concurring) ("[W]hether claims meet the demands of 35 U.S.C. § 101 is a threshold question, one that must be addressed at the outset of litigation," which will have "a number of salutary effects."). A § 101 inquiry is properly raised at the pleadings stage if it is apparent from the face of the patent that the asserted claims are not directed to eligible subject matter. *See Berkheimer v. HP Inc.*, 881 F.3d 1360, 1368 (Fed. Cir. 2018) ("Patent eligibility has in many cases been resolved on motions to dismiss."); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1360 (Fed. Cir. 2017). Moreover, claim construction is not required to conduct a § 101 analysis. *Genetic Techs.*, 818 F.3d at 1374. And a court need not individually address claims not asserted or identified by the non-moving party if the court identifies a representative claim and "all the claims are substantially similar and linked to the same abstract idea." *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat. Ass'n*, 776 F.3d 1343, 1348 (Fed. Cir. 2014) (internal quotation marks omitted).

B. Claims Must Be Dismissed If Not Supported by Plausible Facts

"[A] plaintiff's obligation to provide the 'grounds' of his 'entitle[ment] to relief' requires more than labels and conclusions, and a formulaic recitation of the elements of a cause of action will not do." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 555 (2007); *see Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). "[A] complaint must do more than allege the plaintiff's entitlement to relief. A

complaint has to 'show' such an entitlement with its facts," *Fowler v. UPMC Shadyside*, 578 F.3d 203, 211 (3d Cir. 2009), which must rise "above the speculative level." *Twombly*, 550 U.S. at 555. To plead patent infringement, a complaint must allege facts making it plausible that the accused instrumentality "practice[s] each of the limitations found in the [] asserted claims." *See, e.g.*, *N. Star Innovations, Inc. v. Micron Tech., Inc.*, 2017 WL 5501489, at *1-2 (D. Del. Nov. 16, 2017).

C. Prosecution History Estoppel Bars Use Of Doctrine Of Equivalents

A party may allege patent infringement either literally or under the doctrine of equivalents ("DOE"). *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 35 (1997). DOE applies if either: the accused product performs "substantially the same function in substantially the same way to obtain the same result" or the accused product or process is not substantially different from what is patented ("the insubstantial differences test"). *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 866 (Fed. Cir. 2017). Because DOE "can create substantial uncertainty about where the patent monopoly ends," the Supreme Court has "acknowledged that competitors may rely on the prosecution history, the public record of the patent proceedings" for clarity. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 727 (2002).

Accordingly, prosecution history estoppel is invoked where a patentee makes a narrowing amendment to secure allowance during prosecution. *Id.* at 736. Where the amendment "narrow[s] [patentee's] claims, this prosecution history estops [patentee] from later arguing that the subject matter covered by the original, broader claim was nothing more than an equivalent." *Id.* at 727. Narrowing amendments bar a patentee from asserting amended limitations are infringed under DOE by practicing the subject matter an amendment was made to avoid. *Id.* Pertinent here, estoppel applies with particular force where "the examiner's Reasons for Allowance make clear that the examiner and the applicant understood that the invention requires [the added limitation]." *ACCO Brands, Inc. v. Micro Sec. Devices, Inc.*, 346 F.3d 1075, 1079 (Fed. Cir. 2003).

V. ARGUMENT

A. The Claims Of The Patents Are Invalid Under § 101

1. The Focus Of The Asserted Claims Is Entirely On Natural Phenomena

"For an application of an abstract idea to satisfy step one [of the *Mayo* framework], the claim's focus must be on something other than the abstract idea itself." *BSG Tech LLC v. Buyseasons, Inc.*, 2018 WL 3862646, at *4 (Fed. Cir. Aug. 15, 2018). The asserted claims here are focused on nothing other than natural phenomena stemming from donor-specific cell-free nucleic acids circulating in a transplant recipient's body. Ex. B, at 6:61-64 ("Studies reveal that much of the circulating nucleic acids in blood arise from necrotic or apoptotic cells…"); 7:40-46 ("[A]s cell-free DNA or RNA often arises from apoptotic cells, the relative amount of donor-specific sequences in circulating nucleic acids should provide a predictive measure of on-coming organ failure in transplant patients…"); *see also* section III.B above. These cell-free nucleic acids appear as the natural result of a transplanted organ's cells dying (*i.e.,* apoptosis), which happens increasingly when there is organ rejection, dysfunction, or failure. *Id.* As such, detecting or correlating the presence of a donor's cell-free nucleic acids in the transplant recipient's circulation to transplant status is nothing more than observing a natural phenomena.

The asserted claims here begin and end with those natural phenomena. *Ariosa*, 788 F.3d at 1376 ("The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring."). For example, '652 patent claim 1 element (a) starts with "a sample comprising cell-free nucleic acids from a subject who has received a transplant," and element (d) ends with "diagnosing, predicting, or monitoring a transplant status or outcome of the subject … by determining a quantity of the donor cell-free nucleic acids based on the detection of the donor cell-free nucleic acids and subject cell-free nucleic acids…" in the sample. Ex. B, at 27:41-43; 27:59-63. For the '497 patent, claim 1 preamble starts with "detecting donor-specific

circulating cell-free nucleic acids in a solid organ transplant recipient," and ends in element (d) with "determining an amount of donor-specific circulating cell-free nucleic acids from the solid organ transplant in the biological sample…" Ex. A, at 28:2-3; 28:24-26; 28:26-29.

These claims parallel those found ineligible in *Mayo*, *Genetic Techs.*, and *Ariosa*.[4] For example, in *Mayo*, the Supreme Court found the claims ineligible because they "set forth laws of nature - namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of [] drug will prove ineffective or cause harm." *Mayo*, 566 U.S. at 77. Here the '652 patent claims likewise merely recite relationships between amounts of circulating donor-specific cell-free nucleic acids in the organ recipient and corresponding transplant status.

Similarly, in *Ariosa*, the alleged invention was only that "paternally inherited [cell-free fetal DNA] is to be found in maternal blood (using established detection techniques)." *Genetic Techs*, 818 F.3d at 1376 (referencing *Ariosa*). Again, the '497 patent claims are no different, reciting only established techniques to detect donor-specific cell-free nucleic acids in the transplant recipient. And like here, the *Ariosa* inventors applied only "a combination of known laboratory techniques" to amplify and detect paternally inherited cell-free fetal DNA already in the mother's blood. *Ariosa*, 788 F.3d at 1373. As the Court should here, in *Ariosa* the Federal Circuit held the claims were invalid because they were merely "directed to detecting the presence of a naturally occurring thing or a natural phenomenon, [cell-free fetal DNA] in maternal plasma or serum." *Id.* at 1376; *see also Genetic Techs* 818 F.3d at 1375-76 (finding that, like here, "the claims are directed to matter that is naturally occurring," and the method involved "no creation or alteration of DNA sequences").

[4] *See also Cleveland Clinic*, 859 F.3d at 1361 (detecting enzyme in order to diagnose cardiovascular risk); *23andMe, Inc. v. Ancestry.com DNA, LLC*, 356 F. Supp. 3d 889, 904 (N.D. Cal. 2018) (detecting correlation that exists in nature).

2. The Additional Elements Do Not Add Enough For Patentability

The asserted claims add no inventive concept "sufficient to ensure that the patent in practice amounts to ***significantly*** more than a patent upon the natural law itself." *Mayo*, 566 U.S. at 73. To the contrary, like the claims found ineligible in *Mayo*, "the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* That is insufficient to confer patentability. *See, e.g.*, *Ariosa*, 788 F.3d at 1373, 1377-78; *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 764-65 (Fed. Cir. 2014).

For the Court's convenience, Ex. C includes a table identifying, for each claim element, excerpts from the Patents disclosing the routine and conventional nature of the techniques recited. These disclosures are also summarized below.

(a) The Independent Claims

Far from providing any new teachings on how to perform the recited steps, novelty in any of the techniques recited, or unconventional combinations thereof, the Patents expressly describe only "conventional" techniques that were and are "known in the art" to carry out the claimed methods. At the outset, the Patents state:

> The practice of the present invention employs, unless otherwise indicated, ***conventional techniques*** of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics and recombinant DNA, ***which are within the skill of the art***.

Ex. B, at 5:36-48 (numerous references omitted). The Patents also identify each and every specific step recited in the claims as "conventional."

For example, as to the steps of "providing a sample" and "obtaining a biological sample" from the transplant recipient ('652 element 1(a) and '497 element 1(c), respectively), the common disclosure states that "[t]o obtain a blood sample, any ***technique known in the art*** may be used…"

Ex. B, at 10:11-12; *id.* at 1:14-17; 6:57-67; 9:4-14; 10:7-10. Similarly, for the "***genotype***" or "***genotyping***" to establish a polymorphism or SNP "profile" ('652 element 1(b) and '497 elements 1(a)-(b), respectively), the Patents disclose that "[g]enotyping of the transplant donor and/or the transplant recipient may be performed ***by any suitable method known in the art*** including those described herein such as sequencing … or PCR." *Id.* at 20:31-37; 13:51-67 ("using ***existing genotyping platforms known in the art***"); 20:31-51; 26:38-41.

The "multiplex sequencing" and "high-throughput sequencing or digital polymerase chain reaction (dPCR)" of '652 element 1(c) and '497 element 1(d), respectively, are disclosed as techniques that "can be performed by sequencing such as whole genome sequencing or exome sequencing," and also "can be accomplished through classic Sanger sequencing methods which are ***well known in the art***." *Id.* at 15:2-8. The Patents further disclose additional techniques well known in the art, including commercial technologies, *id.* at 15:22-52, and others described in the literature, *id.* at 15:53-17:14; *see also id.* at 7:23-28; 9:8-14; 14:58-67;15:22-17:14; 21:5-8.

The methods for "diagnosing, predicting, or monitoring a transplant status or outcome" by "determining a quantity of the donor cell-free nucleic acids" ('652 element 1(d)), and "determining an amount of donor-specific circulating cell-free nucleic acid" ('497 element 1(d)) also are routine. The Patents disclose that "[d]etection, identification, and/or quantification of the donor-specific markers (e.g., polymorphic markers such as SNPs) can be performed using [numerous techniques]… as well as other methods ***known in the art including the methods described herein***." *Id.* at 9:8-14;18:56-19:2 ("Methods for quantifying nucleic acids ***are known in the art***…"); 17:41-18:53; 21:5-9 ("The presence or absence of one or more nucleic acids from the transplant donor in the transplant recipient may be determined by any suitable method ***known in the art including those described herein*** such as sequencing, nucleic acid arrays or PCR.").

The recitation in '652 element 1(d) that "an increase in the quantity of the donor cell-free nucleic acids over time is indicative of" a transplant-related disorder refers to nothing more than the natural phenomenon itself. *See, e.g.*, *id.* at 7:40-46. As to the final '652 patent limitation that "sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for … CAV," assuming *arguendo* that this is not indefinite for purposes of this Motion only, any sensitivity would have to be an inherent feature of the conventional methods used to perform the claim. The patent discloses that as a general matter, "[t]he invention provides methods that [are] sensitive and specific," and describes all embodiments as having sensitivity of at least 56%. *Id.* at 23:31-44; *see also id.* at 5:36-40. The patent also discloses, among other standard techniques, sequencing using the commercially available "Illumina Genome Analyzer," for which "[h]igher sensitivity can be achieved simply by sequencing more molecules, i.e., using more channels," *id.* at 17:12-13, and "sequencing error rate," which "also affects the sensitivity of this technique," can be "systematically lower[ed] … by resequencing the sample template multiple times, as has been demonstrated by Helicos BioSciences," another commercial provider of conventional sequencers. *Id.* at 17:14-15; 17:22-25. Hence, there is no assertion or evidence that these techniques – or sensitivities that naturally result from their use – is unconventional or new.

Finally, '497 patent element 1(d), reciting "wherein the at least one assay detects the donor-specific circulating cell-free nucleic acids from the solid organ transplant when the donor-specific circulating cell-free nucleic acids make up at least 0.03% of the total circulating cell-free nucleic acids in the biological sample," Ex. A, at 29:1-5, again states no more than a natural phenomenon: presence of a certain fraction of donor-specific cell-free nucleic acids in a transplant recipient's circulation. The Patents ascribe nothing unconventional to detection of this by standard techniques. Instead, the Patents state that the commercial Illumina Genome Analyzer is capable of "detecting

donor molecules when the donor fraction is as low as 0.03%." Ex. B at 17:1-3; 17:7-11.

In sum, the Patents do not contend that any of the claimed techniques were new or unconventional, or that there was any challenge associated with using them. In fact, the Patents admit over and over that their techniques are routine, conventional, and well-known.

(b) The Dependent Claims

The Complaint does not allege infringement of any dependent claims of the Patents. Nevertheless, the dependent claims also merely append conventional techniques to natural phenomena, and are thus also directed to unpatentable subject matter.

Claims 2 and 11 of the '652 patent, *id.*, at 28:41-47; 29:5-7, and claim 24 of the '497 patent, Ex. A, at 30:22-24, recite different types of "polymorphisms" assessed in the "polymorphism profile[s]" established during the "genotyp[ing]" step in the respective independent claims. Setting aside the fact that polymorphisms are naturally occurring genetic differences, Ex. B, at 11:24-26, the Patents (as discussed above) disclose that "[g]enotyping of the transplant donor and/or the transplant recipient" to identify these naturally occurring polymorphisms "may be performed by any ***suitable method known in the art including those described herein***." *Id.* at 20:31-33. The Patents further disclose establishing a profile comprising the recited types of polymorphisms. *Id.* at 20:42-51. But the patents do not describe these techniques as unconventional or new.

Claims 6, 17, 18, and 25 of the '497 patent, Ex. A, at 29:17-18; 29:57-59; 30:25-28, recite detecting and analyzing numbers of single nucleotide polymorphisms (SNPs)[5] that are homozygous or heterozygous, or occur at different frequencies in the population. These polymorphisms again are genetic variances that occur naturally, *id.* at 11:22-33, and the claimed methods for detecting them

[5] An individual naturally has a set of genes inherited from its mother, and another from its father. An individual is "homozygous" at a SNP locus when the nucleotide sequences it inherited from mother and father are the same there. An individual is "heterozygous" at a SNP locus when the sequences inherited from mother and father differ there. This, also, is a natural phenomenon.

are "known in the art," Ex. B, at 20:31-33; 20:52-63. The patent also discloses commercial products for this, *id.* at 13:41-67, wherein "[c]ompanies … currently offer both standard and custom-designed TaqMan probe sets for SNP genotyping…," and "[w]ith such a large pool of potential SNPs to choose from, a usable subset of existing or custom probes can be selected to serve as the probe set for any donor/recipient pair." *Id.* at 13:58-67.

Claim 26 of the '497 patent recites "mapping" nucleic acids detected from the sample to a genome sequence of the transplant donor. Ex. A, at 30:29-33. The Patents again concede that this is known in the art, incorporating by reference publications describing it. Ex. B, at Page 2, References Cited ("Fan et al., Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood, Proc Natl Acad Sci USA (Oct. 2008), 105(42);16266-71 …"); 3:3-7; 18:12-14; Ex. D (incorporated Fan publication) at 16266 (describing mapping techniques).

Claims 15 and 16 of the '497 patent recite performing the "genotyping" step prior to, or simultaneously with, "determining" an amount of donor-specific cell-free nucleic acids. Ex. A, at 29:47-55. This step is conventional and routine when detecting disease, as the Patents admit. *E.g.*, Ex. B, at 7:30-32; 20:31-34. The Patents disclose performing "genotyping" before "determining," for example, where "[b]oth the donor and recipient will be genotyped prior to transplantation," but this is a routine medical practice. *Id.* at 13:2-3. And the patent further describes performing them simultaneously as part of genotyping methods "known in the art." *Id.* at 13:15-17.

Claims 3 and 12-16 of the '652 patent, *id.* at 28:49-50; 29:8-20, and claims 2, 9, 12-14, 27, and 28 of the '497 patent, Ex. A, at 29:6-7; 29:25-26; 29:34-46, 30:34-37, recite types of transplants and samples (bodily fluids or nucleic acids) from which the cell-free nucleic acids are obtained. According the Patents, this too is standard and conventional. Ex. B, at 1:14-19; 2:13-16; 6:57-67; 9:4-14; 10:11-12; 13:21-28. And the recitation of nucleic acids (DNA or RNA) as present in various

bodily fluids is, again, merely a recitation of the natural phenomenon itself.

Claims 4-6, and 10 of the '652 patent, *id.* at 28:51-57; 29:1-4, and claims 3-5, 10, 11, and 30 of the '497 patent, Ex. A, at 29:8-16; 29:27-34; 30:42-45, recite standard techniques for sequencing, amplification, and using a computer. It further describes commercially-available techniques, inherent to them. The patent describes all of this as known in the art, and conventional. Ex. B, at 7:23-28; 9:8-14; 14:11-21;14:55-67; 15:8-17:39; 20:31-36; 20:52-56; 24:35-64.

Claims 19-23, and 31-33 of the '497 patent, Ex. A, at 30:1-21; 30:47-62, recite features of sensitivity and error rates inherent in the claims' recited routine techniques. The patent likewise describes these as part of the corresponding knowledge in the art. Ex. B, at 16:57-59; 17:1-11; 17:20-28; 23:31-34; 25:46-63; 26:48-55. And the limitations to percent of donor-specific cell-free nucleic acids present in a sample, again, simply refer to the natural phenomenon itself.

Finally, claims 7-9 of the '652 patent, *id.* at 28:58-67, and claims 7, 8, and 29 of the '497 patent, Ex. A, at 29:19-24; 30:38-41, recite therapeutic treatments. The Patents similarly describe these as routine, generally practiced techniques. Ex. B, at 4:14-17; *id.* at 4:36-38.

Like the independent claims, apart from natural phenomena, the Patents ascribe nothing new to any of the techniques recited to perform the methods in the dependent claims.

(c) The Claims Append Only Conventional Techniques Known In The Art To The Recited Natural Phenomena

As explained above, the claims of the Patents are directed to natural phenomena: donor-specific cell-free nucleic acids in the circulation of an organ transplant recipient, and the relationship of the donor-specific cell-free nucleic acids to organ rejection or failure. Ex. B., at 7:40-46; 8:18-21; section III.B above. The asserted claims require only that these donor-specific cell-free nucleic acids be detected ('497 patent), or quantified to diagnose, predict, or monitor a transplant status or outcome ('652 patent). But the Patents identify nothing novel about the techniques recited to do so.

As in *Mayo*, "the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." 566 U.S. at 73; *see also Genetic Techs.*, 818 F.3d at 1376 ("The inventive concept … cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself."). Nothing in the Patents suggests that those additional steps – or the recited combinations of them – are inventive in any way.

Here, too, this case is analogous to *Genetic Techs*. and *Ariosa*. In both cases, the Federal Circuit held that various "physical steps" such as the "physical steps of DNA amplification and analysis of the amplified DNA," and "PCR to amplify and detect [the cell-free DNA]" were all well-understood and conventional—much like the physical steps of PCR/amplification, sequencing, and others here. *See Genetic Techs.*, 818 F.3d at 1377-78; *Ariosa*, 788 F.3d at 1377. Also instructive is the Federal Circuit's decision in *In re BRCA*, in which the court concluded that the claims, directed to the abstract idea of comparing various DNA sequences, were not saved by the recitation of limitations that did "nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques," such as "detecting," "amplification," and "sequencing." *In re BRCA1*, 774 F.3d at 764 (Fed. Cir. 2014). None of the steps in these cases conferred patent eligibility because they extracted and analyzed natural phenomena in known and conventional ways. The same is true in this case.

Here, the only potential novelty is the presence of circulating donor-specific cell-free nucleic acids in a transplant recipient and the correlation of them to transplant status. But even if these natural phenomena were newly discovered (which they are not) such discovery alone does not make observation of the phenomena using conventional techniques patentable. This is why, in *Ariosa*, the court evaluated whether it was "well-understood, routine, and conventional activity" to combine the

method steps to detect DNA in blood ***generally***, not whether it was routine to apply those steps ***to a sample of maternal cell-free DNA*** (the natural phenomenon at issue there). *Ariosa*, 788 F.3d at 1377. The *Ariosa* court rejected the notion that the ***application*** of well-understood, routine processes to the newly discovered phenomenon rendered the claims patent eligible, concluding that looking at the claimed processes as a whole, "the only inventive component of the processes … is to ***apply those well-understood, routine processes to*** paternally inherited [cell-free fetal DNA], ***a natural phenomenon***." *Id*. at 1375. The same principle applies here, only to a different natural phenomenon – donor-specific cell-free nucleic acids.

B. Plaintiffs' Unsupported '652 Patent Infringement Claim Must be Dismissed

To allege a plausible claim for infringement of the '652 patent, claim element 1(d) requires Plaintiffs to plead facts showing that in Natera's Kidney Test, "sensitivity of the method is greater than 56% compared to sensitivity of current surveillance methods for cardiac allograft vasculopathy (CAV)." *See, e.g.*, *Twombly*, 550 U.S. at 555; *N. Star Innovations*, 2017 WL 5501489, at *1 (granting motion to dismiss for failure to show infringement of every limitation). Plaintiffs have not alleged this, let alone pled facts that plausibly support an infringement claim for this limitation.

As explained in section III.C above, CAV refers to a condition that occurs in connection with ***heart*** transplants. This is unrelated to ***kidney*** transplant rejection, which is the subject of Natera's Kidney Test. Exhibit 8 of the Complaint purports to be a claim chart demonstrating how Natera's Kidney Test satisfies this claim element, but it does not allege any facts to show that the accused test's sensitivity is ***compared*** to that of ***then-current methods*** for surveillance of the ***specific CAV heart*** condition recited in the claim. D.I. 1, Ex. 8, at 7-8.

As explained in section III.C above, the patent discloses only invasive imaging/ ultrasound, as the heart transplant-related measure against which to compare for this. But the complaint makes no allegation that sensitivity of the accused non-invasive method for counting cell-free DNA in

Natera's Kidney Test compares to sensitivity of invasive CAV surveillance methods. Plaintiffs have not pled that Natera literally does this. Nor can they, because not only does it make no sense to compare a kidney transplant test to the monitoring of conditions specific to a transplanted heart, but Natera does not compare the sensitivity of its Kidney Test to ***anything*** when performing it. That is clear from the face of the Complaint—which references and attaches a Natera publication on which Plaintiffs base their allegations. D.I. 1, Ex. 8 at 7-8 (referencing *id.*, at Ex. 9). That publication does not include any comparison of sensitivity of the Natera Kidney Test to anything, much less methods for surveillance of CAV as recited in the '652 patent claims. *Id.*, Ex. 9.

Plaintiffs cannot demonstrate infringement literally, nor can they attempt to capture scope beyond this literal limitation under DOE. As explained in section III.C above, the limitation was added by amendment to overcome prior art, and was a reason the examiner allowed the patent. Prosecution history estoppel bars Plaintiffs from now attempting to recapture this scope—which Stanford expressly disclaimed to obtain the patent—under DOE. *See, e.g.*, *Festo*, 535 U.S. at 727. Here the bar applies with particular force, as the amendment was added to overcome a rejection based on references that use ***sequencing*** techniques just as Plaintiffs allege Natera's Kidney Test practices. *See* Ex. F, at 2-3 of "Detailed Action"; Ex. G, at 5-6. Plaintiffs cannot be permitted to recapture the very scope they surrendered in exchange for securing a patent.

The comparison of sensitivity of the accused Kidney Test to that of surveillance methods for CAV is a critical limitation, made to overcome prior art, and required to obtain issuance of the patent. Plaintiffs have not alleged facts to plausibly show that Natera practices it literally, and they are barred from alleging it under DOE. Plaintiffs' claim must be dismissed.

VI. CONCLUSION

Natera requests that the Court dismiss the Complaint in its entirety with prejudice.

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May 16, 2019

CERTIFICATE OF SERVICE

I hereby certify that on May 16, 2019, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on May 16, 2019, upon the following in the manner indicated:

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